REMARKS/ARGUMENTS

Attached hereto is a new inventorship declaration (including the dated signatures by inventors Peter Jensen and Vladislav Soroka), as required in the Office Action.

By the instant Amendment the hand-written interlineations/markings on specification pages 23, 24, 33, 45, 47, and 61 are deleted, as required in the Office Action. Also, the sequence identifier (SEQ ID NO:) is inserted for each of the sequences found at page 58 of the specification.

A new "Sequence Listing," on paper and in computer readable form (computer diskette), is submitted, concurrently, herewith. As indicated, above, sequences appearing in figures 4, 7, 17, and 20 have been marked with the corresponding SEQ ID NOs.

Claims 98-147, presented hereby in place of claims 56-97, canceled hereby without prejudice or disclaimer, are pending.

Claim 98 corresponds to claim 56 with the wording "and/or the sequence (K/R)-X-X-X-(K/R)-X-(E/D)-(L/I/V/F)-X-(L/I/V/F), wherein X is any amino acid residue, and/or the sequence selected from the group (E/D)-X-(K/R)-(L/I/V/F)-X-(L/I/V/F), (E/D)-X-(K/R)-(L/I/V/F)-(L/I/V/F), (E/D)-X-X-X-X-(E/D)-X-(K/R)-(L/I/V/F), (E/D)-X-X-X-(E/D)-X-(K/R)-(L/I/V/F) or (E/D)-X-X-(E/D)-X-(K/R)-(L/I/V/F)" deleted from the claim.

Claim 102 replaces claims 60 amended by replacing the wording "comprising the sequence K/R-K/R-X-K/R or K/R-X-K/R, wherein X is any amino acid, more suitably the sequence K/R-P-K/R, K/R-K/R-P-K/R, K/R-K/R-E-K/R or K/R-K/R-E-K/R, even more suitably the sequence

K-P-K, K-K-P-K, K-K-E-K or K-K-E-R and most suitably the sequence A-S-K-K-P-K-R-N-I-K-A (SEQ ID NO:1), A-K-K-E-R-Q-R-K-D-T-Q (SEQ ID NO:2), or A-R-A-L-N-W-G-A-K-P-K (SEQ ID NO:3)" with the wording "wherein the amino acid sequence of the compound comprises the sequence K/R_{0-1}-P/E-X-K/R".

The wording of claims 77-85, 92, 93, 95, and 96 has been amended, in corresponding claims 114-122, 129, 130, 132, and 133, respectively, by directing the subject-matter of the claims to a method of treatment.

Presented claims 141 and 142 contain subject matter of claim 61.

Presented claims 143-147 represent subject matter described ion in the instant specification at page 22, lines 14-34.

Claims 67-69 and 74-97 were withdrawn based on a finding of alleged lack of unity of invention under PCT. Applicants maintain traversal of the finding for the reasons of record, i.e., as set forth in their reply filed March 14, 2003.

The PTO should acknowledge – and honor – the finding regarding unity of invention made by the Swedish Patent Office in connection with the PCT application. The decision regarding unity of invention by the Swedish Patent Office was made according to the PCT Rules (not according to the Patent Law of the Kingdom of Sweden). Since the subject patent application represents the PCT application entering the national phase in the United States, the PTO should recognize the finding on unity of invention by the Swedish Patent Office – indeed, as should the patent authority of every PCT-contracting state, when proceeding on the national phase of the PCT application.

Claims 56-66 and 70-73 were rejected under 35 USC 112 for allegedly lacking enablement. Reconsideration is requested.

The present patent application contains a concise written specification of the invention on pp. 22-56 and exhaustively supplemented with a description of the examples of how to make and use the same on pp. 57-76. The both can obviously enable any person skilled in the art to carry on the invention.

Paragraphs 11 and 12, of §112 rejection.

Claims 56-60 in their present wording and claims 70-73 are drawn to an amino acid sequence having at most 12 amino acids from the sequence of the neural cell adhesion molecule NCAM or a mimic thereof comprising the sequence K/R$_{0-1}$-K/R-X-K/R, wherein X is any amino acid, said sequence capable of binding to the Ig1-Ig2 domains of NCAM and of stimulating or promoting neurite outgrowth from NCAM presenting cells and/or proliferation thereof. Accordingly, the present claims relate to a compound having at most 12 amino acids from the sequence of the neural cell adhesion molecule NCAM, wherein the sequence comprises the motif K/R$_{0-1}$-K/R-X-K/R, wherein X is any amino acid, and not just any fragment of NCAM.

Furthermore, in claims 60 and 61 the invention discloses preferred embodiments of such the sequences, namely the sequence A-S-K-K-P-K-R-N-I-K-A (SEQ ID NO:1), which represents C3 peptide, a mimic of the Ig2 NCAM domain, the sequence A-K-K-E-R-Q-R-K-D-T-Q (SEQ ID NO:2), which represents D2 peptide, a mimic of the Ig2 NCAM domain, and the sequence A-R-A-L-N-W-G-A-K-P-K (SEQ ID NO: 3), which represent D4 peptide, a mimic of the Ig2 NCAM

domain (a motif corresponding to the amino acid sequence of claim 56 is marked with bold letters). The invention, however, emphases that the peptides corresponding to SEQ ID NO: 1-3, which are very interesting, for example as a prosthetic nerve guide or for the purpose of medical use (claims 77-97), can also be the tools for identifying peptide ligands comprising the motif of claim 56 (p.27, lines 25-27), which expected to bind to the NCAM Ig1 domain. The specification disclosed on pp. 40-41 and in Table 7 of the present application teaches that peptides comprising the above motif comprising three basic amino acid residues, or a homologue thereof, wherein one basic amino acid residue has been substituted for another amino acid residue, will with a high probability have a stimulating effect on neurite outgrowth or inhibiting effect on cellular aggregation. Accordingly, specification does enable any skilled person how to make or use the invention, since the skilled person is taught about the length of a compound as well as of the motif, two features determining the effect.

¶s 14-17

Applicants do not agree with the Examiner's statement, that "in order to practice the invention the quantity of experimentation required to practice the invention as claimed".

As shown in Figure 7 of the instant application some peptides ("117, 118, 119") have no apparent action, namely the neurite outgrowth promoting effect and inhibition of aggregation of neurons, while others (e. g. C3 (SEQ ID NO: 1), D3 (SEQ ID NO: 2) or D4 (SEQ ID NO: 3)) show strong activity. The Examiner's observation that peptide "117" contains two single amino acid changes from K to A at position 6 and R to A at position 7, which completely obliterate the tested

activities, and the Examiner's extraction from p.41, line 34-35 of the specification, namely "the substitution of only two basic amino acids in the sequence of the C3 (SEQ ID NO: 1) peptide completely abolished the neuritogenic effect", are absolutely correct.

However, it appears that the Examiner completely failed to notice, when cited, that the application contains a detailed guidance (see pp. 25-26-27, lines 34-36, 1-35 and 1-11, correspondingly, and pp. 40-43 of the present patent application) concerning the importance of basic amino acids in the sequence of interesting peptides. The motif K/R_{0-1}-K/R-X-K/R, wherein X is any amino acid, relating to Group I peptides drawn to SEQ ID NO: 1, comprises at least two basic amino acids, substitution of at least one of which with an non-charged (A) amino acid residue resulted in no effect in the tested functional assays (see Figure 7 of the present application).

Thus, in view of the above the Examiner's assumption that "the activity of any given peptide is highly unpredictable" and "one of skill in the art would have been unable to practice the invention without engaging trial and error experimentation" is false. Moreover, it seems very inconsistent that the Examiner draws conclusions concerning activity of peptides drawn to SEQ ID NO: 1 (Group I) from analysis of activity of peptides belonging to Group II and Group III (p.6, lines 5-7), which had previously been considered by the Examiner as non-elected subject matters relating to the present patent application and consequently have been withdrawn from examination.

Further, the Examiner prejudicially claims that "the specification does not provide any guidance or examples that would enable a skilled artisan to make the claimed peptides and mimics of the SEQ ID NO: 1".

The specification does provide a number of examples enabling a skilled artisan to practice the invention. Thus, Examples 3-4 describes the synthesis and screening of resin-bound decapeptide libraries followed by selection of interesting peptides to be synthesised. Example 5 provides a description of the synthesis of peptides. Functional selection of peptides is disclosed in Examples 6-9. A motif, which confers on the peptides an ability to stimulate neurite outgrowth, is disclosed in the invention, therefore, there is no need to synthesise a new peptide library following with screening of the peptides for desirable effect. New peptides comprising the disclosed motif can be synthesised using standard methods, as for example, described in Example 5, and with high expectation of success, screened as described in the application functional assays using suggested concentrations.

The Examiner's conclusion, that "it is not plausible to extrapolate the concentrations and their effects for variants and mimics of SEQ ID NO: 1" is prejudicial as well.

Figures 9-10 of the present patent application demonstrate a dose-dependent effect of the C3 peptide (SEQ ID NO: 1) and two C3 analogues, namely the D3 (SEQ ID NO: 2) and D4 (SEQ ID NO: 3) peptides, on neurite extension in primary hippocampal cell cultures. The peptides demonstrate the same threshold of the effect when used in the same range of concentration. Figure 11 shows the results of an experiment demonstrating the neuritogenic capability of different C3 mutants ("116-119") and a peptide ("121") comprising the discussed above motif. The peptides in the experiment have been used in the same concentration as C3. From the figure it can been clearly seen that three mutants, wherein basic amino acid residues had been mutated to non-polar residue

("117-119") did not have any effect in the cultures, whereas the other mutant and the peptide 121, having this motif, did have the effect comparable to the C3 peptide.

The last mentioned evidence thus provides an additional argument in support to the notion that the present invention is fully enabled in the specification such that the skilled artisan can make and use the same without undue experimentation.

Paragraphs 18-22

The Examiner considered the following references as relevant to illustrate the state of the art in connection with neural cell adhesion molecule NCAM:

Frei et al. (1992) J. Biol. Chem 118(1): 177-192.

Doherty et al. (1995) J. Neurobiol. 26(3): 437-446.

Rao et al. (1992) J. Cell Biol. 118(4): 937-949.

Rao et al. (1994) J. Biol. Chem. 269(44): 27540-27548.

Frei et al. (1992) J. Biol. Chem 118(1): 177-192. The document describes a study showing the involvement of individual extracellular domains of NCAM in execution of diverse functions of the protein. The individual extracellular domains/fragments of NCAM or combined the Ig (IgI-V) or Fn (Fn1-2) domains of NCAM have been expressed as recombinant proteins having molecular masses ranging from 12 to 52 kDa (Fig. 2, p.181:lines1-5) and examined for their functional activity. Table 1 on page 181 summarises the efficacy of the mentioned recombinant NCAM fragments with respect to induction of the functional effects in cells. In particular, "neurite outgrowth" effect was detected only for the Ig 1, Fn1-2 and IgI-V fragments of NCAM.

Difference in effectiveness of large fragments of NCAM described by Frei et al. (1992) cannot be regarded to as indication of unpredictability of efficacy of mimics of a short amino acid sequence consisting at most of the 12 amino acid residues comprising the amino acid sequence K/R_{0-1}-K/R-X-K/R, wherein X is any amino acid.

The invention contemplates only peptides of at most 12 amino acids in length comprising the above motif, which may be a part/fragment of the NCAM Ig2 domain or a mimic of said domain. The peptides of the invention may bind to the Ig2 binding site of the Ig1 domain or to a different binding site on the Ig1 domain. If the binding site is not a "normal" Ig2 biding site, the binding will mimic the normal binding and result in neurite outgrowth and/or proliferation of NCAM presenting cells in the same way (see p.27, lines, 13-21. of the present application). As an example of such mimic the present specification provides a peptide of the sequence A-S-K-K-P-K-R-N-I-K-A (SEQ ID NO:1), C3. Furthermore, the present invention teaches that efficacy of a peptide fragment with respect to induction of the functional effects in cells is dependent on the presence of the motif in the sequence of a candidate peptide, in particular positively charged amino acid residues in the peptide sequence. Thus, a peptide that binds to the NCAM Ig2 domain through a binding site that comprises at least 2 basic amino acid residues should, according to the present invention, comprise at least 2 amino acid residues within a sequence of 10 amino acid residues, more suitably within a sequence of 3 amino acid residues, is considered to be very interesting for the purpose of the present invention (see p.42, lines 29-36, of the present application).

In view of the above explanation the teachings of Frei et al. (1992) J. Biol. Chem 118(1): 177-192, would not be concerned relevant to enablement of the present invention by the skilled artisan.

Doherty et al. (1995) J. Neurobiol. 26(3): 437-446. The document represents a review of up-to-date (March 1995) data concerning the role of the neural cell adhesion molecule (NCAM) in morphological plasticity of the nervous system.

Discussing the ability of different NCAM isoforms to stimulate neurite outgrowth the Examiner refers to the discussion in the document of major NCAM isoforms, which are presented as proteins of 120, 140 and 180 kDa. These NCAM isoforms can bind to the Ig1 or Ig2 domain of NCAM, and some of them can to the extent of stimulating neurite outgrowth, depending on variations in their polypeptide chains, which are effected by alternative splicing or post-transcriptional processing. The document discusses some splice and post-transcriptional modifications of these isoforms, which can influence NCAM-dependent neurite outgrowth.

The present invention features a neurite outgrowth response initiated by the binding to the Ig1 and/or Ig2 NCAM domains of a compound having at most 12 amino acids from the sequence of the neural cell adhesion molecule (NCAM), or a mimic thereof, comprising the sequence K/R_{0-1}-K/R-X-K/R, wherein X is any amino acid, said sequence capable of binding to the Ig1-Ig2 domains of NCAM and of stimulating or promoting neurite outgrowth from NCAM presenting cells.

A mimic of the compound according to the present invention can be selected from molecules represented by peptides, peptide derivatives, antibodies, and non-peptide compounds, such as small

organic molecules (p. 24, lines 30-36 of the present patent application). Large molecules, i.e., comprising an amino acid sequence having more then 12 amino acid residues, comprising the above motif are not included within the scope of the present claims as possible mimics of the compound. Therefore, the NCAM isoforms of 120, 140, and 180 kDa disclosed in Doherty can not be considered as mimics of the compound of the present invention.

Thus, in view of the above explanation the teachings Doherty et al. (1995) J. Neurobiol. 26(3): 437-446, would not be concerned relevant to enablement of the present invention by the skilled artisan.

Rao et al. (1992) J. Cell Biol. 118(4): 937-949. Rao et al. (1994) J. Biol. Chem. 269(44): 27540-27548. These documents both relate to a peptide sequence from the Ig3 domain of NCAM, which is involved in the mechanism of NCAM homophylic binding. Analysing the response of cells to different fragments of the NCAM Ig3 domain, said fragments comprising different parts of the identified sequence, Rao et al. (1992) points to individual amino acid residues of this sequence as having major importance for the binding associated effects. Furthermore, results presented by Rao et al. (1994) teach that a single substitution of an important amino acid in the identified sequence-binding motif can abrogate the functional effect of a peptide comprising the motif. However, the results by Rao et al. (1994) also teach that not all amino acids of the binding motif have the same importance with respect to the binding and its associated effects.

The present invention uses the methodology of Rao et al. (1994), which is well known in the art, namely mutational analysis, to reveal the importance of particular amino acid residues in the

binding motif embodiment of the present invention drawn to SEQ ID NO: 1. All peptides comprising the motif and their mutants having the required residues substituted for other amino acid residues were tested in functional essays and did demonstrate the expected effect. Therefore, the Examiner's conclusion concerning unpredictability of the activity of given peptides is poorly taken.

Moreover, both references contain information that may be considered in favour of the present invention. Thus, Rao et al. (1994) (J. Biol. Chem. 269(44): 27540-27548) teach that only substitutions of the amino acid residues having particular features, hydrophobic residues being the examples provided in the cited reference, can strongly influence binding.

Specific features of the residues required by the present invention is that they are (1) basic and (2) carry a positive charge. However, the references at issue can not be considered as relevant to enablement of the present invention as none of the sequences disclosed by Rao et al. (1992) (J. Cell Biol. 118(4): 937-949) and Rao et al. (1994) (J. Biol. Chem. 269(44): 27540-27548) comprises the motif of the present claims, i.e., the motif recited in present claim 98.

In view of the above discussion it is readily apparent that the skilled artisan, to make and use the present invention to its full scope, would not need to resort to trial and error to determine the peptides and their mimics that have the desired activity, as the present invention teaches the amino acid residues responsible for the desired activity and provides examples of functional tests demonstrating that the teachings are correct.

¶ 23.

The Examiner states that the problem of predicting protein structure from sequence data and in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While this may be true for long-chain proteins, this is certainly not true for peptides of the present invention, which are at most 12 amino acids in length, including the specified motif. As stated above the present specification provides a variety of sequences bearing the claimed motif and having the claimed activity, thereby, showing the variety of possible peptide structures having same activity.

The references:

Wells (1990) Biochemistry 29:8509-8517;

Ngo etal.(1994) The Protein Folding Problem and Tertiary Structure Prediction, pp.492-495;

Bork (2000) Genome Research 10:398-400;

Skolnick et al. (2000) Trends in Biotech. 18(1): 34-39;

Doerks et al. (1998) Trends in Genetics 14:248-250;

Smith et al. (1997) Nature Biothech. 15:1222-1223;

Brenner (1999) Trends in Genetics 15:132-133;

Bork (1996) Trends in Genetics 12: 425-427

are cited to argue the sufficiency, under §112, ¶1, of disclosure for amino acid sequences involved in formation of an active or binding site in NCAM for the purpose of teaching a skilled artisan to determine, without undue experimentation, positions in the protein (NCAM) that are tolerant to

change, and the nature and extent of changes, that can be made to these positions to observe the effect of binding to this site.

The cited documents all relate to the problem of protein-structure-function relationships, and they feature difficulties in predicting protein function from the sequence/structure data of a given protein.

Thus, Wells (1990) (Biochemistry 29:8509-8517) analyses the effects of different single and multiple mutations on protein function. The document discusses a discrepancy between the effects of distant and interacting mutations.

Ngo et al.(1994) (The Protein Folding Problem and Tertiary Structure Prediction, pp.492-495) is addressed to the computational complexity of protein-structure prediction. The reference discusses different theories and algorithms, which had been up-to-date used in different approaches to solve the problem.

Bork (2000) (Genome Research 10:398-400) points out limitations in the computational prediction of qualitative features of proteins based on the sequence data presented in public sequence databases, because of the insufficient quality of the data presented.

Skolnick et al. (2000) (Trends in Biotech. 18(1): 34-39) discusses the weakness of "sequence-to-function" and "sequence-to-structure-to-function" approaches in prediction of the function of a protein. The "sequence-to-function" approach, which is based on using barely the sequence data, has led to significant function-annotation errors in the sequence databases. An alternative approach "sequence-to-structure-to-function" has been proven to be more efficient in

protein-function assignment. The document, however, mentions the fact that most up-to-date predicted models are better at describing the geometry of the core of the molecule than in its loops and, so, precisely predicting the function of a protein whose active site is in the protein loops is doubtful. Despite a number of limitations of the latter approach, the reference still teaches that protein-function prediction based on protein-structure data is useful in obtaining deeper insight into the biological mechanism of protein function and regulation.

Doerks et al. (1998) (Trends in Genetics 14:248-250) provides some functional annotation for a number of poorly or uncharacterised proteins using protein sequences from different sequence databases. The document notices the difficulties in assigning functions to the proteins by sequence similarity (by automatic prediction), emphasising that most of the software robots used for the purpose are erroneous.

Smith et al. (1997) (Nature Biothech. 15:1222-1223) discusses the inconsistency in nomenclature of protein sequences in public databases.

Brenner (1999) (Trends in Genetics 15:132-133) shows the lack of accurate referencing of gene sequences to their functional annotation in public sequence databases.

Bork (1996) (Trends in Genetics 12: 425-427) discusses the high degree of error in sequences presented in public sequence databases.

All of these cited references are of little or no relevance to with respect to enablement of the subject-matter of the present invention, since none of the references teaches the structure-function relationship of small peptides such as presently claimed.

The present invention provides a compound having at most 12 amino acid residues taken from the amino acid sequence of NCAM, or a mimic thereof having an amino acid sequence of at most 12 amino acid residues, wherein said amino acid sequence comprises the specified motif. The present specification (see pp. 40-43), including a number of working examples (see Example 7, figs. 7 and 11) provides sufficient enablement with respect to the structural features necessary in order to obtain the claimed activity. The guidance provided undoubtedly enables the skilled artisan to make and use the presently claimed invention in its full scope without undue experimentation

According to the present invention a compound selected from the group of peptides drawn to SEQ ID NO: 1 (Group I) is not necessarily involved in formation of an active-binding site in the NCAM protein. The compound of the present invention is directed to binding wild-type NCAM protein, as said protein expressed is in living organisms. NCAM polypeptides having a mutated binding site for the compound of the invention are off interest of the present patent application. Therefore, the documents discussed above can not be considered as relevant to enablement of the present invention, as the present invention does not relate to structure-function relationships of NCAM protein or mutations affecting NCAM function, *per se*.

¶ 24.

The present invention does not relate to *any* amino acid sequence having at most 12 amino acid residues taken from the amino acid sequence of the neural cell adhesion molecule (NCAM). The amino acid sequence derived from NCAM according to the present invention comprises the motif of the formula K/R_{0-1}-K/R-X-K/R, wherein (only) X is "any" amino acid. There are, therefore, a

limited number of NCAM fragments no more than 12 amino acids length comprising this motif, such that enablement is not in question. In the sequence of human NCAM 140, comprising 848 amino acids (shown in Figure 17 of the present application), for example, the motif K/R_{0-1}-K/R-X-K/R is repeated only 8 times, among which the preferred motif K/R-P-K/R is present only once. Therefore, for example, from among all the fragments shown in Fig. 25 of the subject application, the compound of the present claims, being drawn to a fragment of the Ig2 NCAM domain, can only be selected from fragments of the sequence comprising amino acid residues 143 to 165.

Thus, the Examiner's statement, that the breadth of the claims fails to recite limitations for what (allegedly) constitutes enabled peptides and mimics, and that undue experimentation would be required of the skilled artesian to make and/or use the presently claimed invention in its full scope, is not well taken

Claims 56 and 60 were rejected under 35 USC 112, ¶2, for allegedly being indefinite. Reconsideration is requested.

With respect to claim 56, the allegation that the term "at most" renders the claim indefinite is incorrect. The correct test for indefinite claim language is whether one of ordinary skill in the art would be confused as to the scope of subject matter defined by the language at issue. *In re Kroekel*, 183 USPQ 610 (CCPA 1974). Applying this test demonstrates that the language at issue satisfies the requirements of 35 USC 112, ¶2.

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Replacement Sheets of Proposed Drawings Corrections

ATTACHMENT

The amino acid sequence of a compound of the invention comprises from 3 to 12 amino acid residues. It is apparent that the sequence can not be less then 3 amino acid residues and, at the same time, meet the limitation to at least ("from") "3" amino acid residues. This is only common sense. The range of peptide having a size from 3 to 12 amino acid residues can not, therefore, be termed "ill-defined" for purposes of §112. ¶2, since the skilled artisan would be confused as to the scope of subject matter defined by the language at issue. *Kroekel.*

With respect to claim 60, the wording of the claim is amended, as present claim 102, according to Examiner's recommendations.

Accordingly, for the foregoing reasons the rejections of record, under §112, ¶1, and under §112, ¶2, are in order for withdrawal.

Favorable action is requested.

Respectfully submitted,

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